Chair's Summary: Mechanisms of Exacerbation of Lung Diseases

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Abstract

This year's conference focused on the origins of exacerbations in chronic lung diseases, such as asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and cystic fibrosis. Common themes emerged, with the role of viral infections being key. In addition, there were data presented supporting the role of the microbiota and microbial dysbiosis either in the gut or in the lung contributing to disease progression and the susceptibility to disease exacerbation. These effects can be amplified by the triggering of biologic cascades that include alterations in oxidative stress and inflammatory mediator release, which can be driven by epithelial cell injury or activation.

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Exacerbations in Asthma

The major role of viruses (especially rhinovirus [RV] species) in asthma exacerbation was reviewed and underlined by this year's keynote speaker, Sebastian Johnston, one of the first to have identified this fact. These exacerbations seem to be clearly more severe in uncontrolled asthma. It has been shown that a local defect in type I or III IFNs or a reduced Th1 response can lead to increased viral replication in patients with asthma. This defect in type I or III IFNs may be due to antagonism of IFN receptor signaling by the suppressor of cytokine signaling 1 that can be induced by IL-13 as well as by virus infection itself. The release of the type 2 proximal cytokines, IL-25 or IL-33, is also induced by viruses, which can further increase asthma exacerbation severity through IL-13 release by group 2 innate lymphoid (ILC2) cells. IL-25 has been shown to be an important molecule in murine models of virus-induced exacerbation, whereas IL-33 seems to be more critical in human studies to date. These observations should open up new therapeutic approaches that could be implemented soon after the start of viral infections in an effort to mitigate the severity of the exacerbation.

The role of oxidative stress is not yet fully understood, and René Lutter showed that the baseline oxidative stress correlates strongly with decline in lung function in preclinical chronic obstructive pulmonary disease (COPD) and asthma models. The level of reactive oxygen species predicted the decline in lung function, whereas the level of Nrf2, a transcription factor that controls the expression of antioxidant genes, was associated with protection. These oxidative stresses can be triggered by viruses, aeroallergens, or pollution. Professor Lutter showed that oxidants impact the liberation of inflammatory mediators by targeting transcription regulators, and examples were shown, such as T-cell–restricted intracellular antigen-1 (TIA1) cytotoxic granule-associated RNA binding protein-like 1.

Microbial dysbiosis has been recognized lately to modulate inflammation of chronic respiratory diseases, and this was discussed by Benjamin Marsland. It was shown that, in a COPD model, microbial dysbiosis quickly ensues, worsening lung disease in an IL-17–dependent fashion, whereas absence of a microbiota protects against disease progression. Findings were also presented showing that a fiber-rich diet ameliorates inflammation in a preclinical house dust mite model of asthma as well. This effect was shown to be related to short-chain fatty acids released by bacteria. These metabolites resulted in decreased eosinophilic responses as well as promotion of the expansion of tolerogenic dendritic cells (DCs) in the lung. These tolerogenic DCs down-regulated allergic reactions without hampering the induction of antiviral $CD8^+$ T cell responses.

Dr. James Gern presented new data on speciation of RVs and that not all RVs are equal. A new group of RVs, RV-C, is most closely associated with severe exacerbation. One receptor used by RV-C is cadherin-related family member 3 (CDHR-3), a tight junction protein that

seems more accessible during type 2 inflammation of the airway. The role of omalizumab to decrease the rate of exacerbation was described with data supporting the notion that a key mechanism of anti-IgE efficacy is through reducing virus-associated exacerbations.

The concept of asthma with a Th2-high and a Th2-low profile was presented by John Fahy. Based on a longitudinal study of more than 150 subjects, it appears that 22% of patients had a persistent eosinophilia in sputa (>2%) and 31% were intermittent with eosinophilia. Persistently, noneosinophilic asthma represented 47% of patients in their cohort. The biomarkers used presently are blood and sputum eosinophilia, and periostin levels in blood. The Th2-high patients were shown to have higher levels of gene expression in their epithelial bushings of genes regulated by IL-13, including periostin, chloride channel accessory 1, and Serpin B2. Then, the results of eight biologic therapies were revisited, showing recent clinical results with mepolizumab (anti–IL-5) and dupilumab (anti–IL-4 Rα) to reduce exacerbations. Lastly, there was discussion on the role of plasmacytoid DCs in controlling viral infection and that the release of type 1 IFN may be disrupted in type 2 allergic asthma. This again supported the concept that Th2 inflammation favors viral-induced exacerbations.

Exacerbations in COPD

The chair of this session was Michael Holtzman, who reviewed the role of the epithelial cell as a key element for chronic airway disease, in particular via the production of IL-33–high progenitor cells in the lung, which, under the pressure of danger signals, will release IL-33, which can act on ILC2 and natural killer T cells. IL-33 results in the release of IL-13, which induces mucous production. This could lead to epithelial reprograming, which may drive disease even the absence of continued exposure to noxious agents, such as smoke.

Yasmin Thanavala reported on immune dysfunction in patients with COPD. The importance of epithelial injury by smoke, respiratory pathogens, or danger-associated molecular patterns was again highlighted. Dr. Thanavala presented data on the presence of increased levels of T regulatory cells (T-regs), myeloid-derived suppressor cells, as well as evidence for programmed cell death 1 $(PD\text{-}1)^+$ exhausted effector T cells in subjects with COPD compared with healthy subjects. These T-regs were apparently protective of lung function degradation and were more suppressive than T-regs from healthy control subjects. Blockade of PD-1 and cytotoxic T-lymphocyte–associated protein 4 resulted in significant augmentation of T cell IFNγ production. Thus anti–PD-1 may show promise as a new target to manage COPD exacerbation. Further preclinical studies in this area are needed.

In contrast, Farrah Kheradmand showed that activated lymphocytes are present in the lung of smokers. T cell stimulation by lung elastin fragments correlates with the severity of emphysema. The phenotype of frequent exacerbators was shown to be associated with increases in autoreactive T cells. The activation of complement (C3a in particular) was shown to activate antigen-presenting cells, which have an increased capacity to stimulate Th1 and Th17 responses, while dampening $CD4^+$ T cell peripheral tolerance.

Richard Boucher reviewed the general pathophysiologic scheme for mucous impaction and hyperconcentration in cystic fibrosis (CF) and COPD. The nature of periciliary liquid is described with the various tethered mucins, MUC1, -4, and -16, whereas the mucous layer contains soluble Muc5B. The evidence of static mucous, as seen in epithelial sodium channel transgenic mice, is proinflammatory. This phenotype was maintained even when mice were rederived germ free, suggesting that mucostasis is proinflammatory *per se*. Viruses like respiratory syncytial virus (RSV) were shown to increase mucin secretion *in vitro*. The patchy nature of mucous clearance is likely a key factor during CF or COPD exacerbations.

Homer A. Boushey discussed the vicious cycle of injury, inflammation, and infection in the airways of COPD exacerbations. The variability across subjects' sputa in bacterial diversity was shown. The role of viral infection, in particularly RV infections, was shown to induce changes in the sputum microbiome. More interestingly, the data collected in the airway microbiome before, during, and after COPD exacerbations were shown. The impact of oral steroids, antibiotics, or both was shown at five time points for 12 subjects. The exacerbation treatments were shown to have very different impacts on the microbiome, in particular inhaled corticosteroids. Interestingly some species of bacteria are typical COPD pathogens and contribute to exacerbations, whereas certain microbiome members seem to contribute to functional homeostasis in COPD airways.

J.-A. Wedzicha reviewed important clinical data in COPD exacerbations with the frequent initial role of viral infections more or less followed by bacterial superinfection. The role of irritants was also discussed. The increased number of exacerbations seen in more severe COPD of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort study was discussed as well as the correlation between biomarkers, such as fibrinogen, C-reactive protein, and serum amyloid A. The possibility of frequent exacerbators becoming infrequent exacerbators in 39% of cases after 1 year was also mentioned. The minimal effect of steroid withdrawal in the prevention of exacerbations and the additive efficacy of long-acting β2 stimulants with anticholinergics as bronchodilators was also presented. Finally, the number of exacerbations as a marker of healthcare decline was pointed out in some detail.

Mechanism of Exacerbations in Idiopathic Pulmonary Fibrosis

In the introduction to the session, Melanie Königshoff set the stage with an overview of pathogenesis of fibrotic lung disease and the role of repeated injury of the epithelium that can initiate idiopathic pulmonary fibrosis (IPF) in the setting of appropriate genetic factors, leading to the release of chemokines to recruit fibroblasts as well as factors able to activate fibroblasts. She reviewed the IPFnet criteria of 2007, where exacerbations were defined essentially as an intrinsic, idiopathic manifestation of IPF in the absence of other factors. However, recent accumulated evidence suggests that acute respiratory worsening in patients with IPF might be caused by occult infection, gastroesophageal reflux, surgery/mechanical ventilation, and other external noxious stimuli that should be accounted for. She pointed out that, unlike COPD and asthma, there is an accelerated IPF

biology (such as epithelial cell injury, collagen deposition) during exacerbation of IPF.

The topic of genetic variants and outcome of idiopathic fibrosis was discussed by Ivana Yang with an emphasis on the regulation of MUC5B. MUC5B expression is controlled by common single-nucleotide variants in the promoter as well as by DNA methylation. This expression is enhanced in diseased areas in the IPF lung with the promoter activity associated with MUC5B expression in small airways. To understand this complex regulation of gene expression, there are a number of studies in process, including RNA and DNA sequencing. To date, the group has identified at least two clusters of differentially expressed genes associated with molecular subtypes of IPF—one group of genes in extracellular matrix and host defense, including, matrix metalloproteinase (MMP) 1, MMP7, MMP13, lipocalin, BPI fold containing family A, member 1 (PLUNC), as well as MUC4, -5B, and -16. Another cluster shows changes in expression of genes that control cilia, whereas genome-wide association in various idiopathic interstitial pneumonias show an association of common genetic variants with host defense genes, such as ATP11, cell adhesion genes, such as desmoplakin and dipeptidyl-peptidase 9, as well as those genes controlling telomere length: telomerase RNA component (TERC), telomerase reverse transcriptase (TERT), and oligonucleotide/oligosaccharide-binding fold containing 1 (OBFC1).

The role of viruses in IPF and IPF exacerbations is not yet clear. Bethany Moore elegantly reviewed the studies with positive and negative correlations in IPF, including the role of hepatitis C, adenovirus, and torque teno/transfusion-transmitted virus. The herpes viruses are a group of viruses that might explain more clearly IPF with lytic or latent viruses. These latent infections could explain focal changes of IPFs, especially in older adults. Some evidence was reviewed that the cytokine, IL-17, which has an ortholog in *Herpesvirus saimiri* (viral IL-17), is detected at the transcript level in IPF lung; thus, this cytokine could be playing a role in IPF. The role of infections in driving IPF exacerbations remains to be further defined.

Luca Richeldi discussed that 40% of patients with IPF die of exacerbations. He has argued for a new definition of IPF exacerbation: acute respiratory worsening of IPF resulting from acute lung injury. The role of nintedanib to reduce exacerbations has been revisited per adjudication of INPULSIS trials suggesting a greater decrease of acute exacerbations in patients with an FVC of less than 70% of predicted value.

Exacerbations in CF

The chair, James F. Chmiel, reviewed the pathophysiology of CF, the function of CF transmembrane conductance regulator, and the consequences of the disease on mucous plugging, infection, and inflammation due to defective innate and additive immunity leading to bronchiectasis. The importance of the number of exacerbations as a predictor of lung function decline was also reviewed.

Felix Ratjen described that pulmonary exacerbations are indeed clinically meaningful events. Inflammation in the lung begins early in life. There is increased RV replication in bronchial epithelial cells carrying functional CF transmembrane conductance regulator mutations compared with non-CF cells, which is associated with reduced type I IFN production. Drugs that target mucous clearance, such as DNase and hypertonic saline, both reduce exacerbation frequency. Interestingly, azithromycin has been shown to reduce exacerbation frequency in patients with CF that are negative for *Pseudomonas aeruginosa*. In addition to a past exacerbation itself, both serum c-reactive protein and sputum neutrophil elastase levels predict future exacerbations of CF.

Michael Surette showed the age-specific prevalence of respiratory pathogens in CF with data collected from the Canadian Cystic Fibrosis registry since 2011. A state of the art review on the microbiome in CF was presented that revealed the presence of conventional CF pathogens, but he pointed out that half of the genera were also made up of obligate anaerobes (i.e., *Prevotella* species). This increase in anaerobes seems to be a signature of the disease. It was shown that a decreased diversity of the microbiota correlated with decreased lung function. Data were shown that infections/exacerbations are polymicrobial in CF, and that organisms can act synergistically with the primary pathogens to enhance virulence without a change in bacterial load. Although much effort has been recently put on 16s sequencing to define the CF microbiome, Dr. Surette made the point that many of the microbial components of the CF lung could be cultured either aerobically or anaerobically, if time and effort were put in place to assure appropriate sample collection and processing by microbiology laboratories. ■

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